OPEN ACCESS

Low serum thyroid-stimulating hormone levels may be an early predictor of sepsis

Peng Li,[1] Yi Lu ,[2] Shu-Bin Guo,[1] Jun-Yu Wang,[3] Jun Yang[1]

[1]Beijing Key Laboratory of Cardiopulmonary Cerebral Resuscitation, Department of Emergency, Beijing Chao-Yang Hospital Capital Medical University, Beijing, China
[2]ICU, Peking University Third Hospital YanQing Hospital, Beijing, China
[3]Department of Emergency, Beijing Chao-Yang Hospital Capital Medical University, Beijing, China

Correspondence to
Dr Jun Yang, Beijing Key Laboratory of Cardiopulmonary Cerebral Resuscitation ;Department of Emergency, Beijing Chao-Yang Hospital Capital Medical University, Beijing 100020, Beijing, China; yangjun26@sina.com

PL and YL are joint first authors.

Received 11 October 2022
Accepted 25 November 2022

To cite: Li P, Lu Y, Guo S-B, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: [please include Day Month Year]. doi:10.1136/spcare-2022-004027

ABSTRACT

Objective This study aimed to explore whether thyroid-stimulating hormone (TSH) plays an early warning role in detecting progression of bacterial infection to sepsis and can serve as a novel marker for the diagnosis of sepsis.

Method This was a prospective study of patients treated for 'bacterial infection' in the emergency department of Beijing Chaoyang Hospital from 1 January 2021 to 31 August 2021. Subjects were divided into a sepsis group (SG) and a non-SG (NSG), according to whether their condition had progressed to sepsis within 72 hours of admission. Routine blood test results as well as biochemical and thyroid function indices (T4, FT4, T3, FT3) were recorded at the time of admission. TSH, Acute Physiology and Chronic Health Evaluation II scores and Sequential Organ Failure Assessment scores were likewise documented.

Results A total of 62 patients were enrolled, the SG and the NSG showed significant differences in their levels of TSH. The results indicate that TSH is an early warning marker for sepsis.

Conclusions TSH plays an early warning role in the diagnosis of bacterial infection progressing to sepsis, having a strong predictive value.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The role of activation and regulation of the nerveendocrine–immune network in the diagnosis of sepsis has received increasing attention. The hypothalamic–pituitary–target gland axis is the main focus, and elucidating its impact on the diagnosis, treatment and prognosis of sepsis has become the target of research efforts.

WHAT THIS STUDY ADDS

⇒ In this study, we analysed the relationship between the serum levels of the thyroid hormones, namely, thyroxine (T4), free T4 (FT4), triiodothyronine (T3) and free T3 (FT3), and thyroid-stimulating hormone (TSH) and the occurrence of sepsis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The inflammatory response caused by acute infection can affect the positive and negative feedback regulatory pathways of the pituitary–thyroid axis, which manifests as abnormality in TSH levels in the early stages. TSH can be used as an indicator of the occurrence of early presepsis.

BACKGROUND

Sepsis refers to life-threatening organ dysfunction caused by host response imbalance triggered by an infectious process.[1 2] It is clear that the identification of diagnostic markers with high sensitivity and specificity in the early stage of the disease is an important measure to reduce diagnostic delays and improve diagnostic accuracy.[3] The hypothalamic–pituitary–target gland axis is the main focus and has become the target of research efforts.[4] In this study, we analysed the relationship between the serum levels of the thyroid hormones, namely, thyroxine (T4), free T4 (FT4), triiodothyronine (T3) and free T3 (FT3), and thyroid-stimulating hormone (TSH) and the occurrence of sepsis.

MATERIALS AND METHODS

This was a single-centre, prospective, observational study and included patients with acute infectious diseases admitted to the Emergency Clinical Research Center of Beijing Chaoyang Hospital, Capital Medical University. After admission, all patients received anti-infective treatment, fluid resuscitation, treatment for complications, organ support and nutritional support for their primary disease. Patients were evaluated for the presence of sepsis every 24 hours until 7th days after admission. The diagnosis of sepsis was based on the sepsis 3.0 criteria, that is, the presence of infection in addition to a Sequential

Organ Failure Assessment (SOFA) score of greater than 2 points.[1] Patients were divided into two groups: a sepsis group (SG) and a non-sepsis group (NSG).

Inclusion criteria

(1)Patients whose primary disease is an acute infectious disease. (2) Age >18 years old. (3) The course of the disease is 24 hours or less.

Exclusion criteria

(1) The primary disease requires surgical intervention. (2) Patients with tumours or connective tissue diseases. (3) Patients with long-term use of oral or intravenous hormones. (4) Patients who died within 48 hours after admission. (5) Patients with acute poisoning or oral drugs that affect thyroid function. (6) Patients who had been diagnosed with sepsis at the time of admission. (7) Patients with a history of pituitary, thyroid or adrenal disease.

Criteria for rejection/withdrawal

(1)Patients who did not complete continuous monitoring for 72 hours for whatever reason. (2) Patients who could not be followed up for sepsis evaluation within 7 days of onset. (3) Death within 28 days unrelated to the primary disease.

Specimen collection and observation

All patients signed an informed consent form after admission and completed the corresponding specimen retention within 4 hours. The following assessments were performed: routine blood test; blood gas analysis; C reactive protein (CRP) level; procalcitonin (PCT) level; serum chemistry; thyroid function and TSH level; Acute Physiology and Chronic Health Evaluation II (APACHE II score); SOFA scoring. Patient evaluation for sepsis using appropriate diagnostic criteria was done every 24 hours until the 7th day after admission. Follow-up was conducted 28 days after the onset of illness and survival was documented. Deaths were classified as either related or unrelated to the primary disease.

Statistical analysis

The SPSS V.23.0 software was used to process the data collected. Normally distributed values were reported as mean±SD. Independent sample t-test was used for comparison between groups. Categorical data were expressed as frequencies (%), and comparison between groups was performed using the (χ^2 test. All data were processed using the binary logistic regression equation, and the OR and 95% 95% CI were calculated. All tests were two-tailed, and a $p<0.05$ was used to determine statistical significance.

RESULTS

A total of 83 patients were enrolled in the study, with 21 did not complete continuous monitoring. Sixty-two patients completed the study, including who were 32 diagnosed with sepsis and 30 without sepsis. The onset of sepsis occurred 1.92±0.58 days after admission in SG. There were no significant difference in age (p=0.767), gender (p=0.770), site of infection (p=0.448, p=0.248 , p=0.410), systolic blood pressure (p=0.614), diastolic blood pressure (p=0.596), average arterial pressure (p=0.289), heart rate (p=0.775), BMI (p=0.404), haemoglobin (p=0.482), platelet count (p=0.937), albumin level (p=0.104), D-dimer level (p=0.366), alkali excess (p=0.110), APACHE II score (p=0.400) and SOFA score (p=0.120) between the two groups. However, PCT level (p=0.034), CRP level (p=0.001), blood lactate level (p=0.000) and 28-day mortality rate (p=0.049) were significantly higher than those in NSG. The levels of T3/T4 (p=0.038) and TSH (p=0.002) in SG were significantly lower than those in NSG (table 1).

Taking the occurrence of sepsis as the end point, the indicators T3/T4, TSH, PCT, CRP and blood lactic acid at admission were brought subjected to the binary logistic regression equation. The results indicate that decreased levels of TSH (p=0.038, OR 1.432, 95% CI 1.020 to 2.011) were independent risk factors for sepsis.

DISCUSSION

The function of the hypothalamic–pituitary–thyroid axis appears to exert a considerable impact on the diagnosis, treatment and prognosis of sepsis.[5 6] This may be because thyroid hormone plays an important role in immune function, especially the innate immune response.[7–11]

Thyroxine has two main forms, T3 and T4. In our research, we found that there was no significant difference in the levels of thyroxine T3, T4, FT3 and FT4 between the two groups (SG and NSG). However, the T3/T4 ratio of the SG was significantly lower than that of the non-septic group. The decrease in the ratio of T3/T4 indicates substantial T3 consumption, with such consumption being closely related to the body's inflammatory response. On one hand, excessive inflammatory reaction leads to the consumption of a large amount of thyroxine, which causes a decrease in blood thyroxine level and can manifest as early hypothyroidism in patients with sepsis. On the other hand, the consumption of a large amount of thyroxine affects the regulatory mechanism of the neuroendocrine–immune network, which leads to reduced regulation of the inflammatory response.

However, the TSH levels of patients in the SG were significantly lower than those in the NSG, and we believe that this change may have more clinical significance. TSH is a hormone that regulates thyroxine release by the pituitary. The phenomenon for TSH level of patients who progressed to sepsis decreased significantly cause that the feedback regulation mechanism of the hypothalamic–pituitary–thyroid axis is disturbed by the acute infection, which then leads to inhibition

Table 1 General condition and clinical characteristics of patients

General condition	Whole (n=62)	SG (n=32)	NSG (n=30)	P value
Age (mean±SD)	74.29±12.43	77.88±12.04	70.47±11.85	0.767
Male (%)	47 (75.8)	25 (40.3%)	22 (35.5)	0.770
Female (%)	15 (24.2)	7 (11.3%)	8 (12.9)	0.710
Dead in 28 days, n (%)	15 (24.2)	11 (17.7)	4 (6.5)	0.049*
Time of onset sepsis (day)	1.92±0.58		–	–
Infection site, n (%)				
Lung infection	49 (79.0)	24 (38.7)	25 (40.3)	0.448
Abdominal infection	6 (9.7)	4 (6.5)	2 (3.2)	0.248
Urinary tract infections	5 (8.1)	2 (3.2)	3 (4.9)	0.410
Skin and soft tissue infections	1 (1.6)	0	1 (1.6)	–
Unknown site of infection	1 (1.6)	1 (1.6)	0	–
Admission vital signs				
Systolic BP mm Hg (mean±SD)	128.69±15.18	129.84±15.60	127.47±14.88	0.614
Diastolic BP mm Hg (mean±SD)	72.00±11.33	73±12.23	70.93±10.39	0.596
MAP mm Hg (mean±SD)	90.90±10.84	91.95±11.43	89.78±10.25	0.289
Heart rate, bmp (mean±SD)	99.03±20.31	101.13±22.19	96.80±18.20	0.775
BMI (mean±SD)	23.19±3.95	22.92±4.22	23.48±3.68	0.404
Laboratory indicators				
Platelets ($\times 10^9$)	218.21±105.40	199.72±108.56	237.93±99.96	0.937
Haemoglobin (g/L)	118.31±28.81	115.91±26.29	120.87±23.30	0.482
PCT (ng/ml)	6.83±21.79	10.20±27.04	3.11±13.43	0.034*
CRP (mg/L)	35.75±124.02	67.25±174.84	7.63±26.66	0.001*
Bundle (g/L)	35.18±6.41	34.36±5.58	36.05±7.18	0.104
D-dimer (mg/L)	4.60±7.51	5.64±8.15	3.44±6.68	0.366
Blood lactic acid	1.91±1.96	2.43±2.58	1.36±0.54	0.000*
Alkali Surplus	−0.24±8.06	−1.14±8.58	0.72±0.01	0.110
Clinical scoring				
APACHE II (mean±SD)	12.98±6.16	14.53±6.68	11.33±5.16	0.400
SOFA (mean±SD)	2.79±2.40	3.28±2.93	2.27±1.55	0.120
T3 (mean±SD)	0.63±0.86	0.51±0.22	0.79±1.28	0.087
T4 (mean±SD)	5.87±2.40	5.93±2.38	5.79±2.47	0.900
FT3 (mean±SD)	1.88±0.55	1.81±0.55	1.96±0.55	0.964
FT4 (mean±SD)	1.13±0.39	1.09±0.29	1.18±0.50	0.372
FT3/T3 (mean±SD)	4.24±2.48	4.37±2.97	4.09±1.70	0.395
FT4/T4 (mean±SD)	0.22±0.19	0.20±0.05	0.25±0.28	0.076
T3/T4 (mean±SD)	0.15±0.45	0.09±0.04	0.23±0.68	0.038*
TSH (mean±SD)	2.54±6.77	1.19±1.02	4.29±10.03	0.002*

*Comparison of sepsis group and non-sepsis group, p<0.05.

APACHEII, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; BP, blood pressure; CRP, C reactive protein; MAP, mean arterial pressure; NSG, non-sepsis group; PCT, procalcitonin; SG, sepsis group; SOFA, Sequential Organ Failure Assessment; TSH, thyroid-stimulating hormone.

of the immune regulatory mechanism. In the case of severe infections, inflammatory factors can reach the pituitary gland through the systemic circulation, causing local vasodilatation, microcirculatory disturbances and metabolite accumulation. This can lead to ischaemic infarction of the pituitary gland and induce pituitary insufficiency.[12 13] Insufficient secretion of TSH negatively affects the synthesis and release of thyroxine, resulting in a lack of the expected increase in thyroxine level during the inflammatory response. Therefore, we have reason to believe that the change in TSH may be closely related to the severity of the inflammatory response caused by infection. The decline in levels of thyroxine due to consumption caused failure of feedback and upregulation of TSH levels, which manifested as persistently low levels of TSH.[14]

Limitations of the study

Due to the limited number of samples in prospective clinical studies, which limits the research conclusion. Moreover, if functional assessment of the hypothalamus–pituitary axis can be further improved, including the measurement of related hormone levels and the nuclear magnetic examination of related parts, it is possible to obtain more reliable research results.

CONCLUSION

The inflammatory response caused by acute infection can affect the positive and negative feedback regulatory pathways of the pituitary–thyroid axis, which manifests as abnormality in TSH levels in the early stages. Because this abnormality is related to the progression of infection to sepsis, TSH can be utilised as an indicator of the occurrence of early presepsis.

Contributors PL, YL, S-BG, J-YW and JY were involved in the conception and study design. PL and YL were involved in the data collection process. S-BG and J-YW designed data collection tools. YL and S-BG cleaned and analysed the data. PL, YL and JY prepared the original draft. All authors contributed to reviewing and editing the final draft. PL is the guarantor of the content.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Beijing Chaoyang Hospital Affiliated to Capital Medical University , Institutional Review Board Number:2021-ke-474. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

ORCID iD

Yi Lu http://orcid.org/0000-0002-8994-8492

REFERENCES

1 Singer M, Deutschman CS, Seymour CW, *et al*. The third International consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801–10.
2 Fleischmann C, Scherag A, Adhikari NKJ, *et al*. Assessment of global incidence and mortality of Hospital-treated sepsis. current estimates and limitations. *Am J Respir Crit Care Med* 2016;193:259–72.
3 Wen X. Effect of early goal-oriented treatment on septic shock in elderly patients and its influencing factors. *Shaanxi Medical Journal* 2019;48:488–91.
4 Hotchkiss RS, Opal S. Immunotherapy for sepsis--a new approach against an ancient foe. *N Engl J Med* 2010;363:87–9.
5 Lin J, Parente JD, Chase JG, *et al*. Development of a model-based clinical sepsis biomarker for critically ill patients. *Comput Methods Programs Biomed* 2011;102:149–55.
6 Fliers E, Bianco AC, Langouche L, *et al*. Thyroid function in critically ill patients. *Lancet Diabetes Endocrinol* 2015;3:816–25.
7 Xiaoyan Y, Jianou Q. Evaluating value of thyroid hormone and procalcitonin and C-reactive protein in patients with sepsis. *Chinese Journal of Experimental and Clinical Infectious Diseases(Electronic Edition)* 2016;10:162–5.
8 Soehnlein O. Neutrophil research, quo vadis? *Trends Immunol* 2019;40:561–4.
9 Datta D, Scalise P. Hypothyroidism and failure to wean in patients receiving prolonged mechanical ventilation at a regional weaning center. *Chest* 2004;126:1307–12.
10 Perrotta C, Buldorini M, Assi E, *et al*. The thyroid hormone triiodothyronine controls macrophage maturation and functions: protective role during inflammation. *Am J Pathol* 2014;184:230–47.
11 Montesinos MdelM, Pellizas CG. Thyroid hormone action on innate immunity. *Front Endocrinol* 2019;10:350.
12 Rimmelé T, Kellum JA. Clinical review: blood purification for sepsis. *Crit Care* 2011;15:205.
13 Peng Z, Singbartl K, Simon P, *et al*. Blood purification in sepsis: a new paradigm. *Contrib Nephrol* 2010;165:322–8.
14 Mebis L, Debaveye Y, Ellger B, *et al*. Changes in the central component of the hypothalamus-pituitary-thyroid axis in a rabbit model of prolonged critical illness. *Crit Care* 2009;13:R147.